Advanced Organic Synthesis
Chem 640

Dr. Nabila Al-Jaber

njaber@ksu.edu.sa

1437-1438

1. *Various text sources*

i. F. A. Carey and R. J. Sundberg, Advanced Organic Chemistry, Part B Reactions and Synthesis 5th edition, Plenum Press: New York, 2007.

ii. M. B. Smith., Organic Synthesis, 2nd edition, McGraw Hill, Inc, 2001.

iii. Bernard Miller, Advanced Organic Chemistry, Reaction, Mechanisms 2nd edition Pearson Education, Inc., 2004

iv. J. March, Advanced Organic Chemistry, Reaction, Mechanism and Structure 2nd edition Mc Graw-Hill 1997.

What is Organic Synthesis?

a) ***Cornforth's definition***: Intentional construction of molecules by means of chemical reactions.

What is Organic Synthesis?

b) Cammers' 3-part definition

i. Plan intentional construction of molecules retrosynthesis

ii. Convince a funding agency or a supervisor that the work can be done and is worth doing

iii. Carry out the laboratory work.

1. The last step does not happen until the first two do.

2. This part is very labor intensive.

The main focus of this course is on the planning and the convincing

Retrosynthetic analysis

is a technique for solving problems in the planning of organic syntheses. This is achieved by transforming a target molecule into simpler precursor structures without assumptions regarding starting materials. Each precursor material is examined using the same method. This procedure is repeated until simple or commercially available structures are reached.

- The ***power of retrosynthetic*** analysis becomes evident in the design of a synthesis.

- The ***goal of retrosynthetic*** analysis is structural simplification. Often, a synthesis will have more than one possible synthetic route.

- ***Retrosynthesis*** is well suited for discovering different synthetic routes and comparing them in a logical and straightforward fashion.

- ***A database*** may be ***consulted at each stage*** of the analysis, to determine whether a component already exists in the literature. In that case, no further exploration of that compound would be required.

Synthesis is Championship, human against nature, the order you do things in is all important with known method.

Synthesis is the process of making a desired compound using chemical reactions. More often than not, more than one step is involved.

What does it take to be a good synthetic chemist?

a) Read the literature and memorized it particularly

1) Keep a deck of index cards on interesting reactions

2) Memorize which reactions to use for retrosynthetic transformations

What does it take to be a good synthetic chemist?

- b) Have a general interest in chemical transformations.

1) Care about how mechanisms are determined

2) Know the principles of stereochemical control

What does it take to be a good synthetic chemist?

b) Have a general interest in chemical transformations

3) Know something about biochemistry and why people make molecules.

4) Consider concepts like molecular strain and what this means for reactivity.

Why do people synthesize organic molecules?

i. Prove structure of a natural product

ii. Prove if it can be done.

iii. Gain insights to reactivity based on structure

iv. Test synthetic methodology

v. physical organic chemical studies

b) Synthesis is done for all of the above reasons and to

i. Construct nanostructure.

ii. Apply or test a biological utility or theory

iii. Gain enough synthetic knowledge of the molecular architecture of natural product x to be able to make analogues for drug testing

c) Knowing how to make molecules is not enough just like knowing how to speak and write is not enough — you have to have something worthwhile about which to speak or write

d) To do this you need to know something about chemistry and science that can often be far away from synthesis

iii. The invention of chromatography meant that the synthetic chemist no longer has to plan syntheses around molecules that are more likely to crystallize ... great! Mean also that oils were recovered and oils are inherently less pure than crystals.

The importance of synthesis

- Total synthesis of interesting and/or useful natural products.

- Industrially important compounds

- compounds of theoretical interest

- structure proof

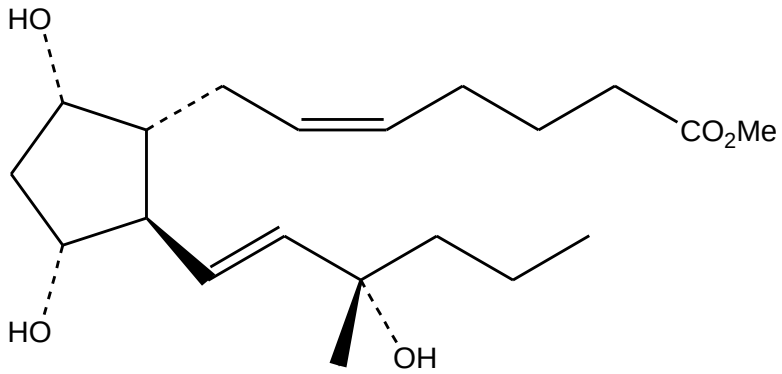
The importance of synthesis

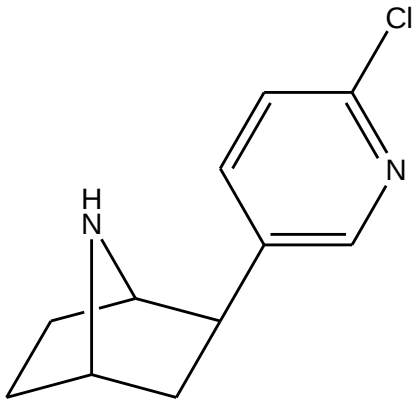
- development of new synthetic methodology

- importance to other areas of science and technology

Examples

Natural products *eg*. steroids, prostaglandins, alkaloids





Prostaglandin1 5-Methyl PGF2α

7-[3,5-Dihydroxy-2-(3-hydroxy-3-methyl-hex-1-enyl)-cyclopentyl]-hept-5-enoic acid methyl ester

< 15 mg isolated from 750 frogs

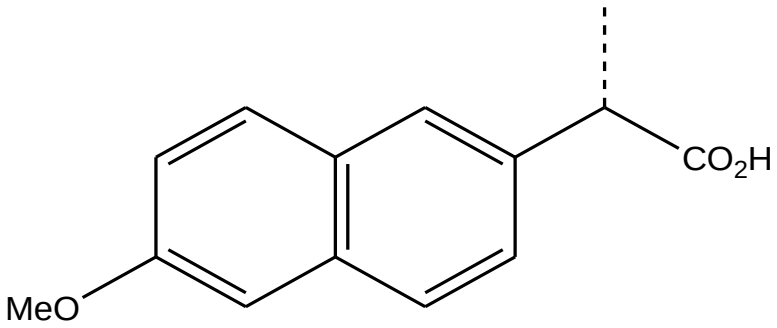
Epibatidine (1*R*,2*R*,4*S*)-(+)-6-(6-chloro-3-pyridyl)-7-azabicyclo [2.2.1] heptane.

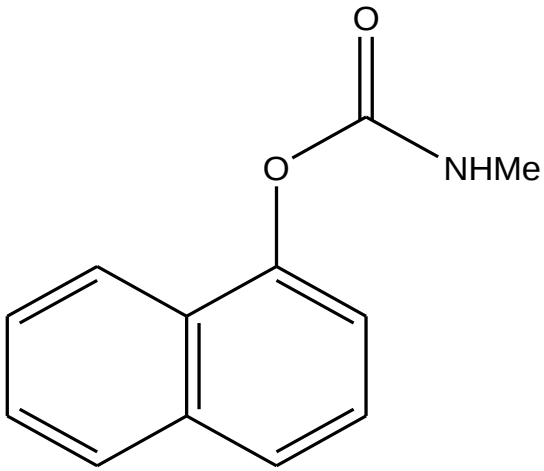
(South American frog alkaloid)

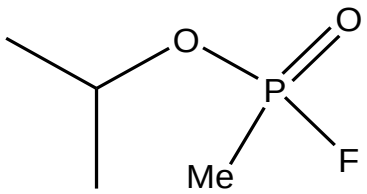
Epibatidine

- is an alkaloid that originally is found in the skin of a neotropical poisonous frog, *Epipedobates tricolor*, found in Ecuador.
- It was initially isolated by John Daly at the National Institutes of Health, and was found to be a powerful analgesic, ~200 times the potency of morphine
- Several total syntheses have been devised due to the relative scarcity of epibatidine in nature

Industrially important compounds such as pharmaceuticals, agrochemicals, flavors, dyes, cosmetics, monomers and polymers

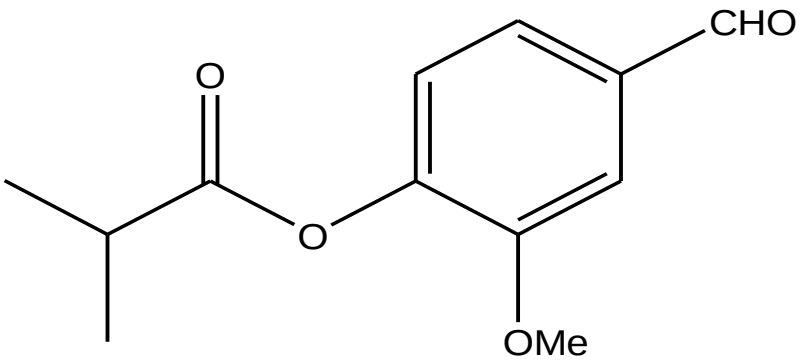




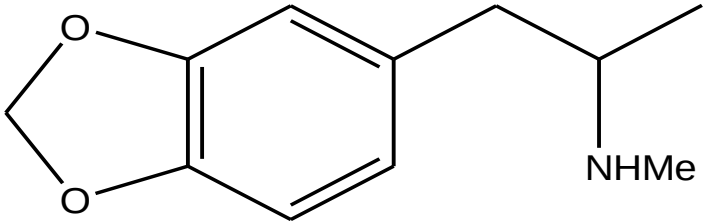


Naproxen (painkiller) *Carbaryl (insecticide)* *Sarin (nerve gas)*

Isobutavan (smells of mint chocolate)



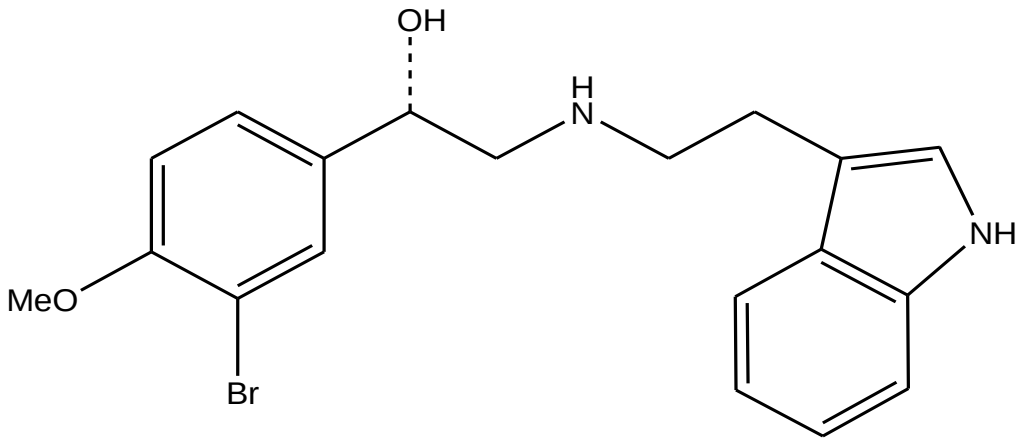
(Ecstasy)



Methylenedioxy methamphetamine, MDMA

Structure proof

While spectroscopy and crystallography are used to determine molecular structures, unambiguous total synthesis is still important



S-(+)-Chelonin B (marine sponge alkaloid)

New methodology

New ways to make molecules, improvement of existing ways, ways of doing what was previously impossible.

Science and Technology

Materials with special applications; molecular switches, non-linear optics, nanotechnology

8. Basic Steps of Solving Synthetic Problems

1) Choice of TARGET MOLECULE (**TM**)

2) Consideration of applicable synthetic methodology

3) Design of synthetic pathway

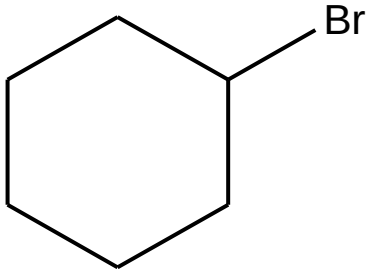
4) Execution of the synthesis

—these steps are highly interactive

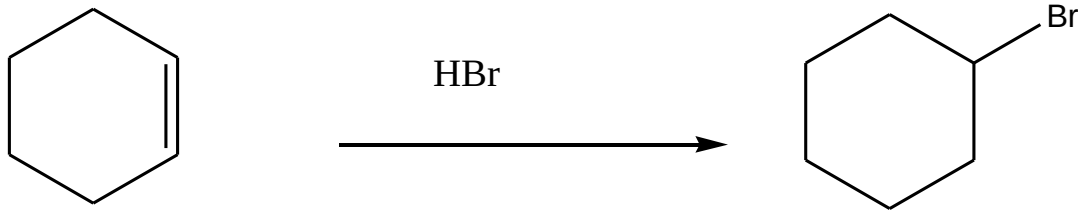
Approaching the design of a synthesis (Part One)

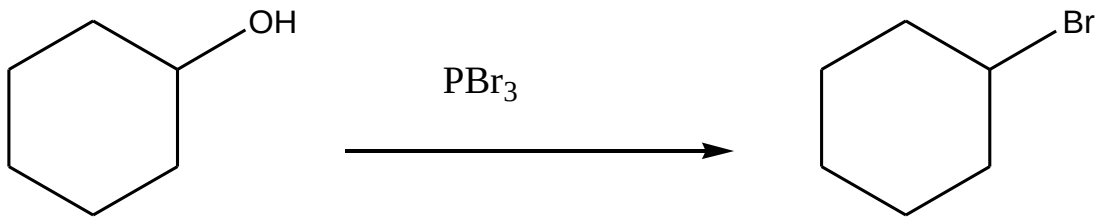
For simple molecules it can be obvious just by looking at the target structure, for example:

Cyclohexyl bromide

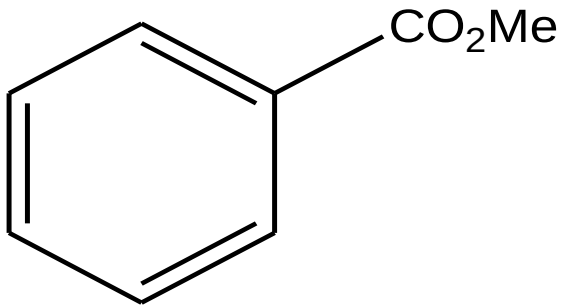


Bromoalkanes are available from alkenes or from alcohols

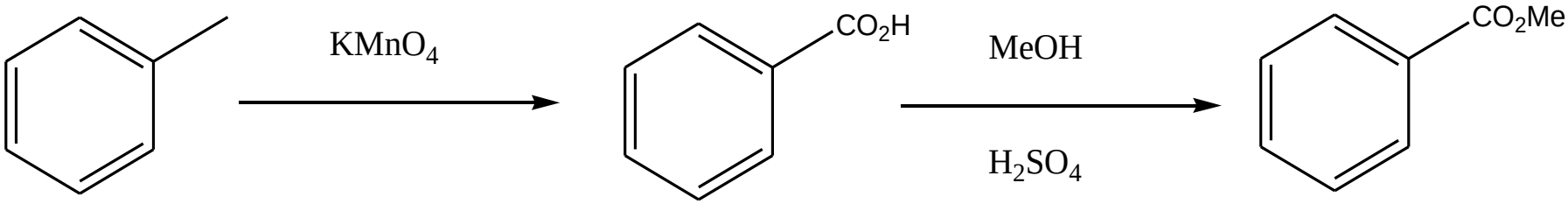




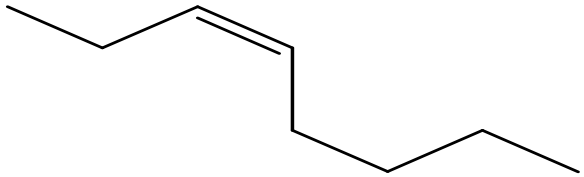
Methyl benzoate



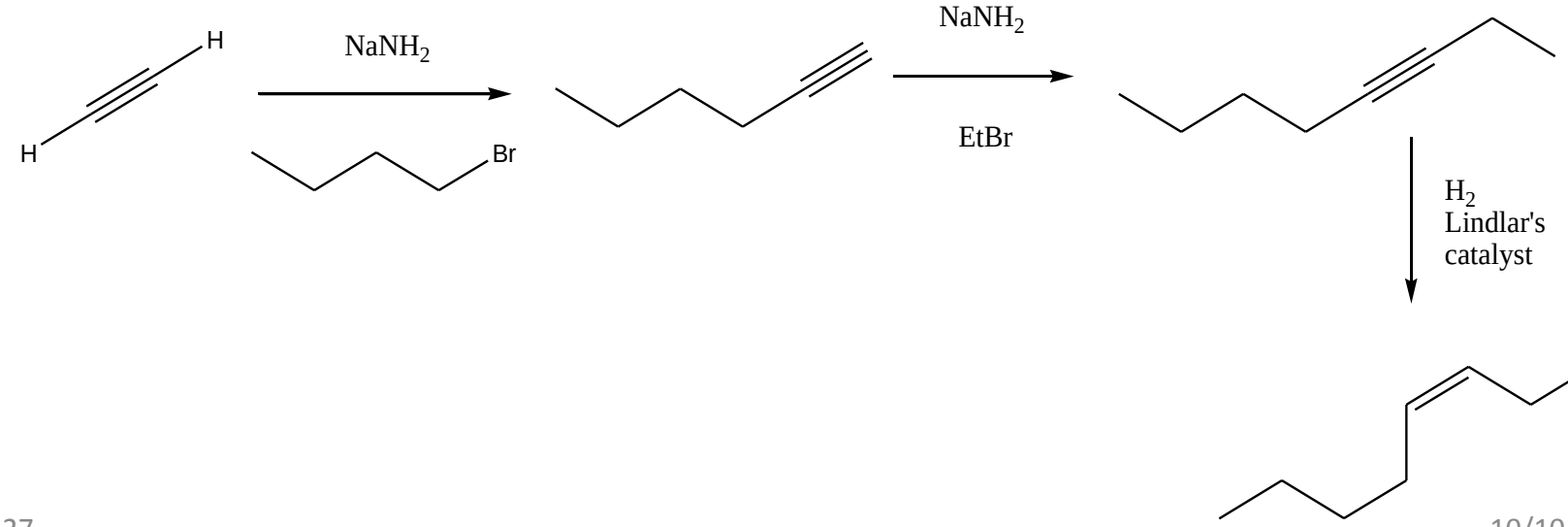
Esters are available from carboxylic acids by reaction with alcohols; benzoic acid is available from toluene



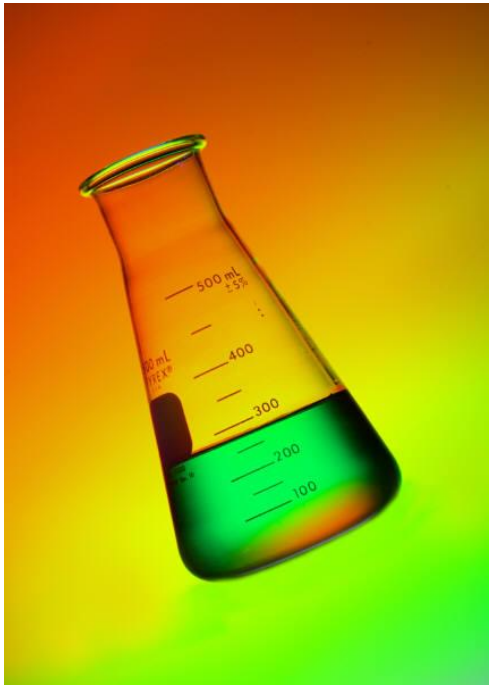
cis-3-octene



cis-Alkenes can be selectively prepared by partial reduction of alkynes; alkynes are accessible *via* acetylide chemistry.



Retrosynthetic thinking



DEFINITIONS

TARGET MOLECULE (TM)	what you need to make
RETROSYNTHETIC ANALYSIS	the process of deconstructing the TM by breaking it into simpler molecules until you get to a recognisable SM
STARTING MATERIAL (SM)	an available chemical that you can arrive at by retrosynthetic analysis and thus probably convert into the target molecule
DISCONNECTION	taking apart a bond in the TM to see if it gives a pair of reagents
FUNCTIONAL GROUP INTERCONVERSION (FGI)	changing a group in the TM into a different one to see if it gives an accessible intermediate
SYNTHON	conceptual fragments that arise from disconnection
SYNTHETIC EQUIVALENT	chemical that reacts as if it was a synthon

Retrosynthetic thinking

a) Working the problem in reverse

b) Each step has a sole criterion:
the problem should get simpler

c) Conformation and molecular shape
cannot be ignored in retrosynthetic analysis

Retrosynthetic thinking

i. You need to know what you are up against

ii. Don’t underestimate the problem! Evaluate the structural complexity at the appropriate level!

Retrosynthetic thinking

iii) Simplicity versus complexity

a) In order to know which direction to go in, you must know what makes a molecule complex.

b) We are going to spend some time in discussing retrosynthesis

Approaching the design of a synthesis

For more complex molecules, it helps to have a formalized, logic-centered approach.

RETROSYNTHETIC ANALYSIS

Retrosynthetic analysis is the process of working backwards from the target molecule to progressively simpler :molecules by means of

DISCONNECTIONS and/or FUNCTIONAL GROUP

http://www.youtube.com/watch?v=-vT6KGCqQO8&feature=related

INTERCONVERSIONS

That correspond to known reactions. When you've got to a simple enough starting material (like something you can buy [and usually is cheap]) then the synthetic plan is simply the reverse of the analysis. The design of a synthesis needs to take into account some important factors.

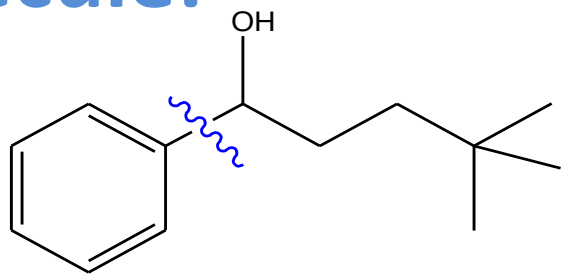
INTERCONVERSIONS

important factors :

1. it has to actually work in general,
2. it should be as short as possible
3. each step should be efficient
4. side products (if formed) and impurities (there always are) should be easily separable from the desired product
5. environmental issues may be relevant

Example retrosynthetic analysis

Target molecule:

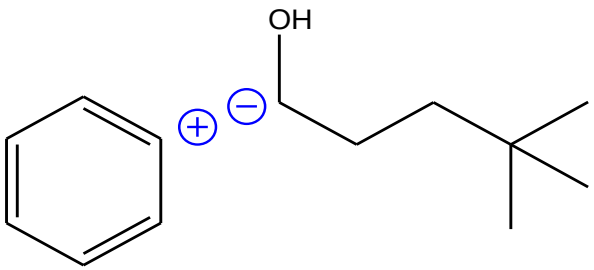


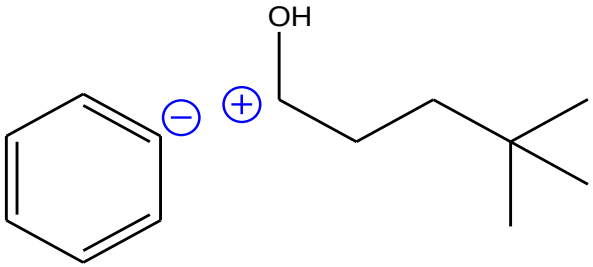
DISCONNECT

A

B

SYNTHONS





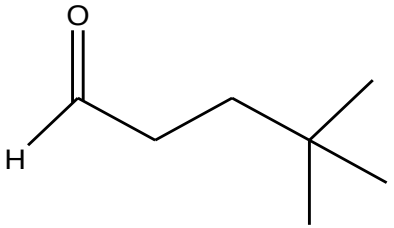
SYNTHONS

REAGENTS

?

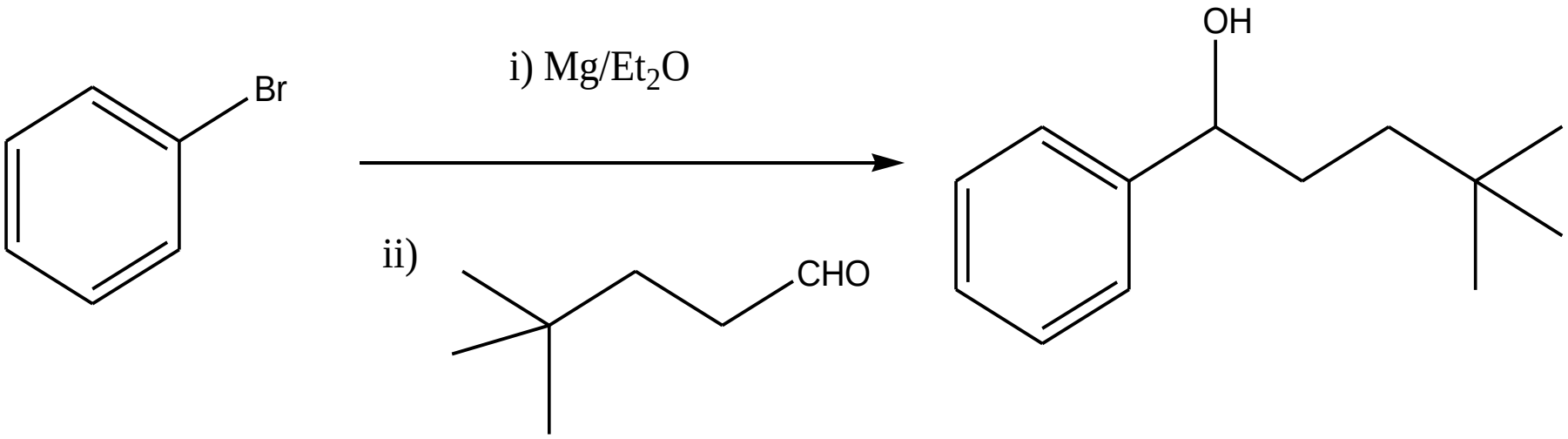
?

PhMgBr



REAGENTS

Therefore the target molecule could be synthesized as follows:

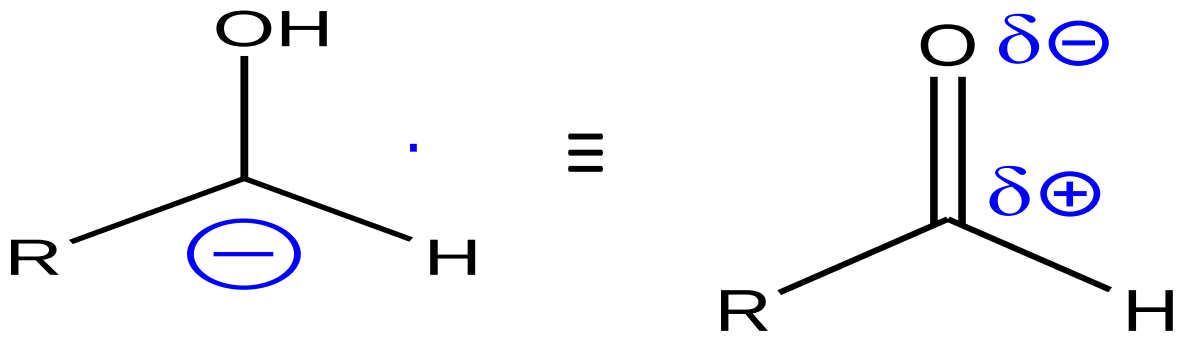


What is a synthon?

When we disconnect a bond in the target molecule, we are imagining a pair of charged fragments that we could stick together, like Lego® bricks, to make the molecule we want.

These imaginary charged species are called SYNTHONS.

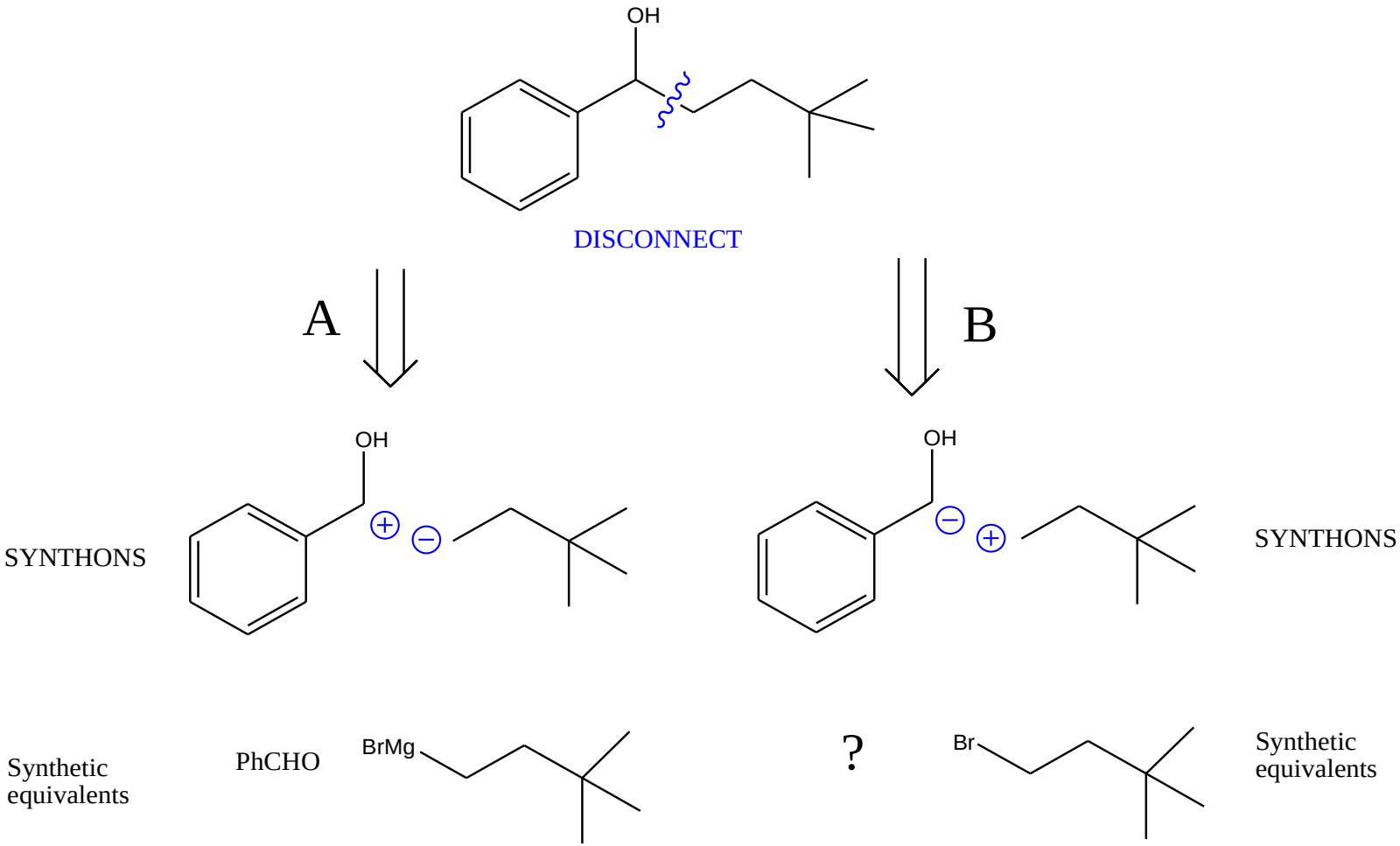
When you can think of a chemical with polarity that matches the synthon, you can consider that a SYNTHETIC EQUIVALENT of the synthon. Thus,



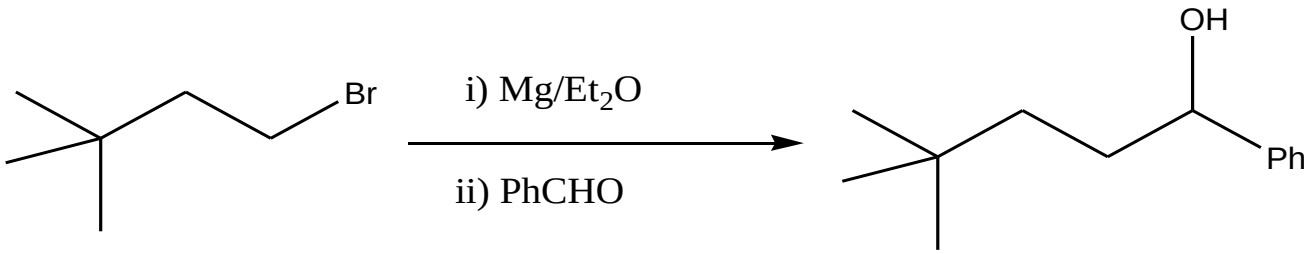
An aldehyde is a synthetic equivalent for the above synthon.

There can be more than one synthetic equivalent for a given synthon, but if you can't think of one...try a different disconnection.

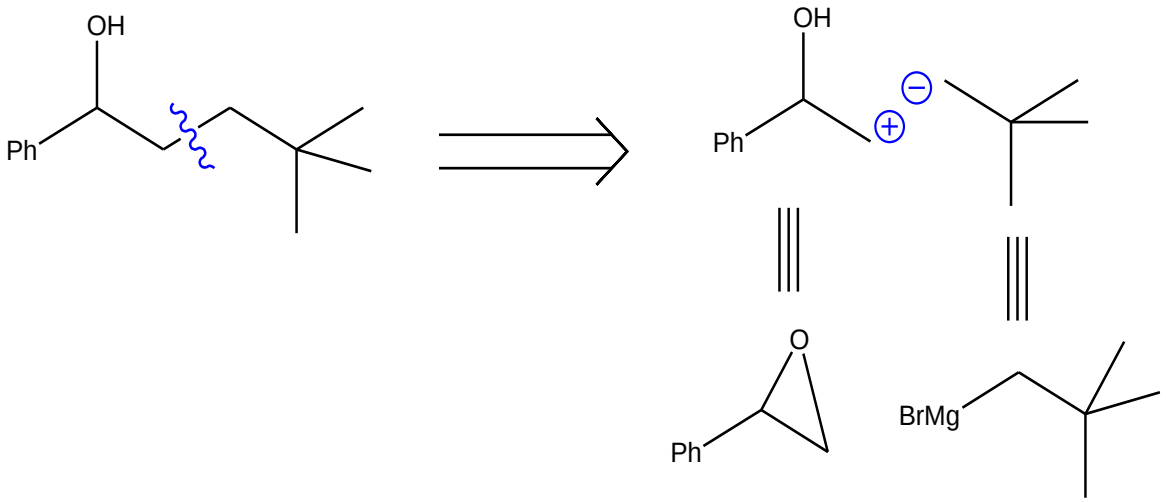
Always consider alternative strategies.



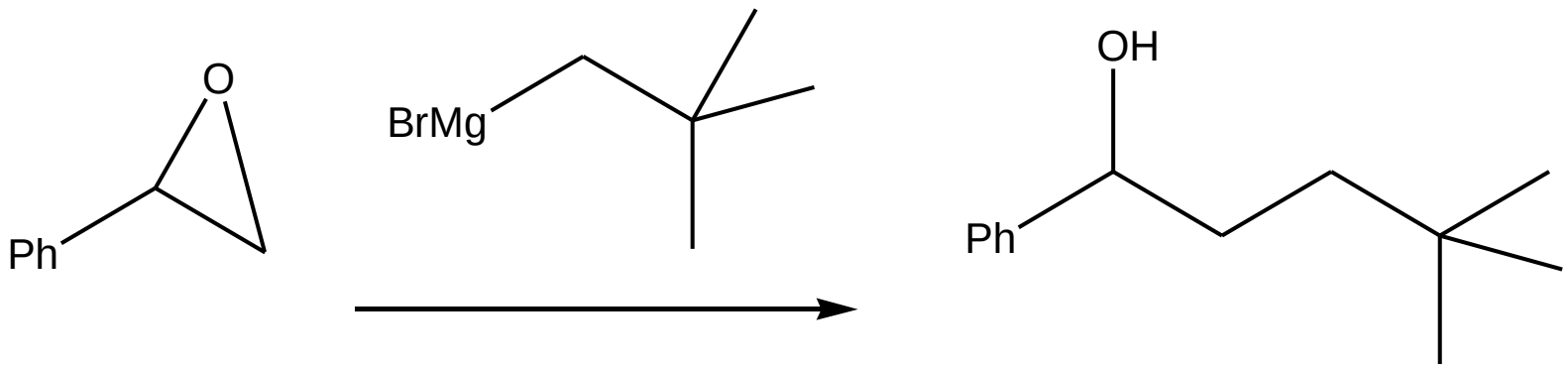
a second possible synthesis:



Similarly



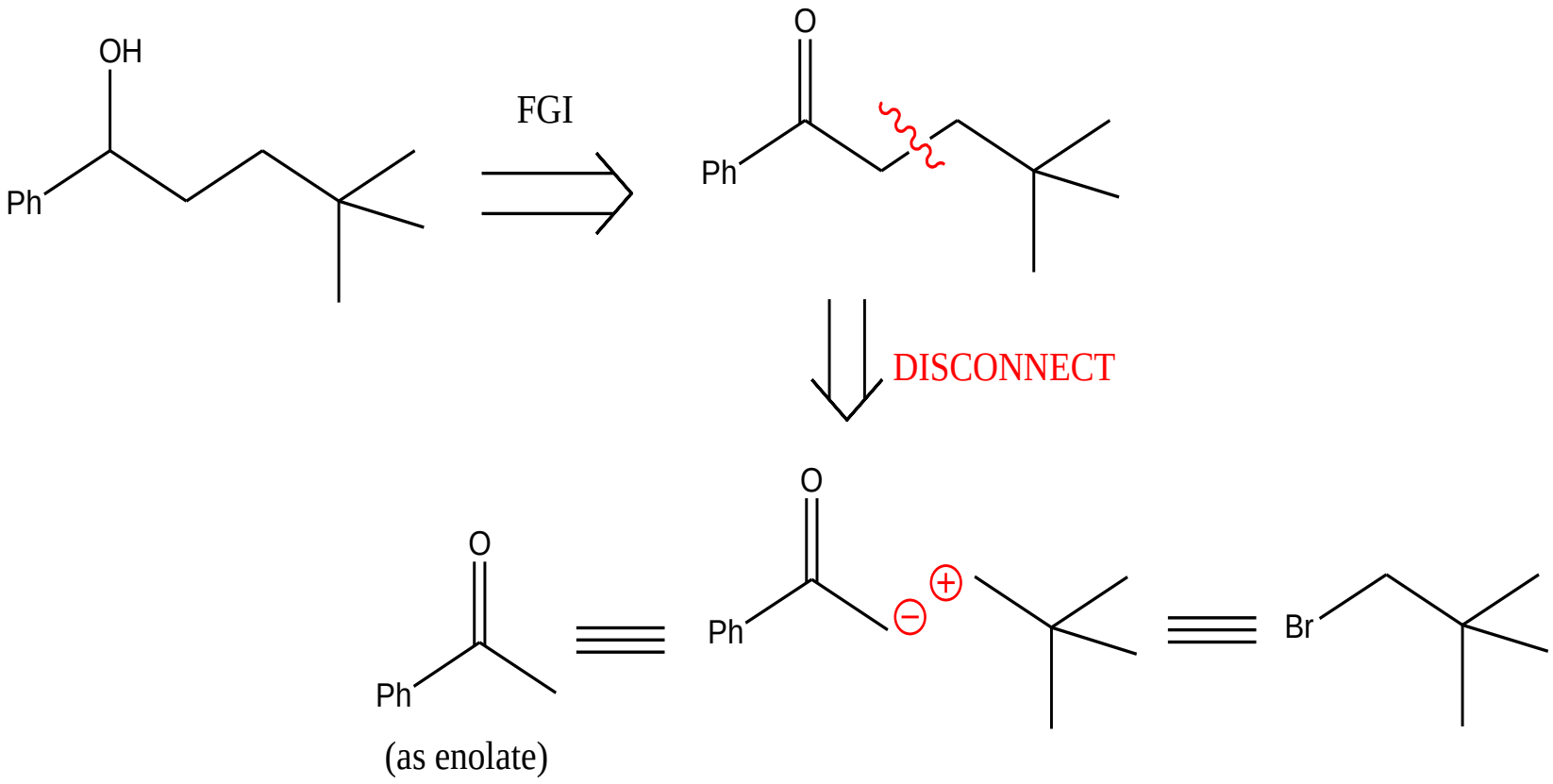
thus a third possible synthesis is



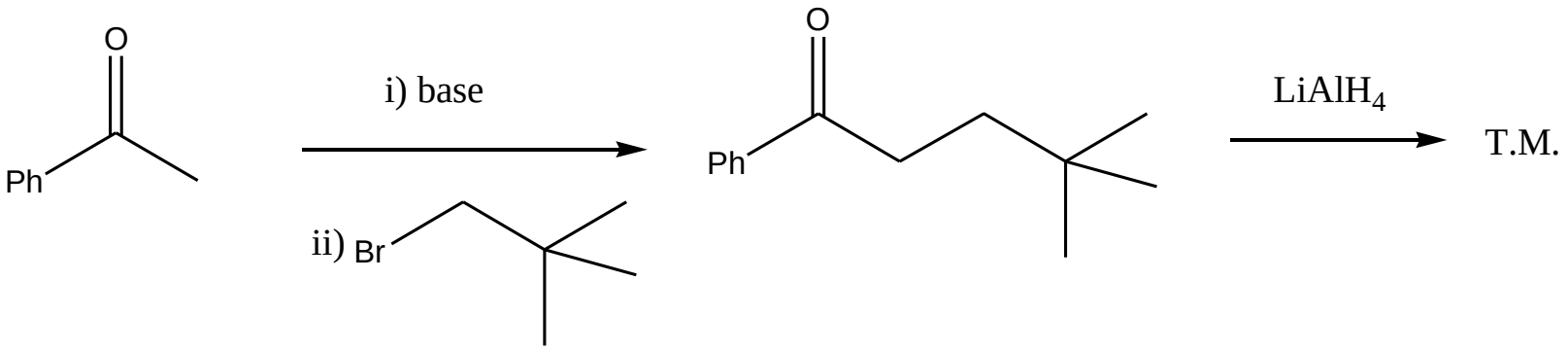
Besides disconnections, we can also consider functional group Interconversion (FGI).

Our target molecule is a secondary alcohol, which could be prepared by reduction of a ketone.

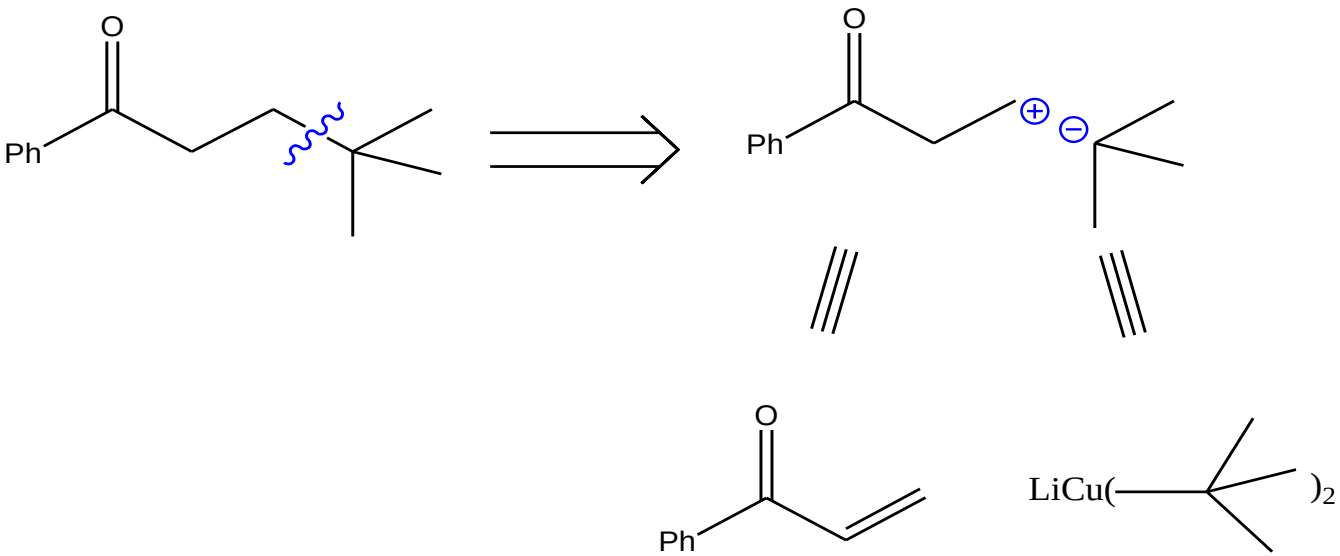
This is represented as follows:


OH
Ph
FGI
O
Ph
DISCONNECT
O
Ph
(as enolate)
O
Ph
Br

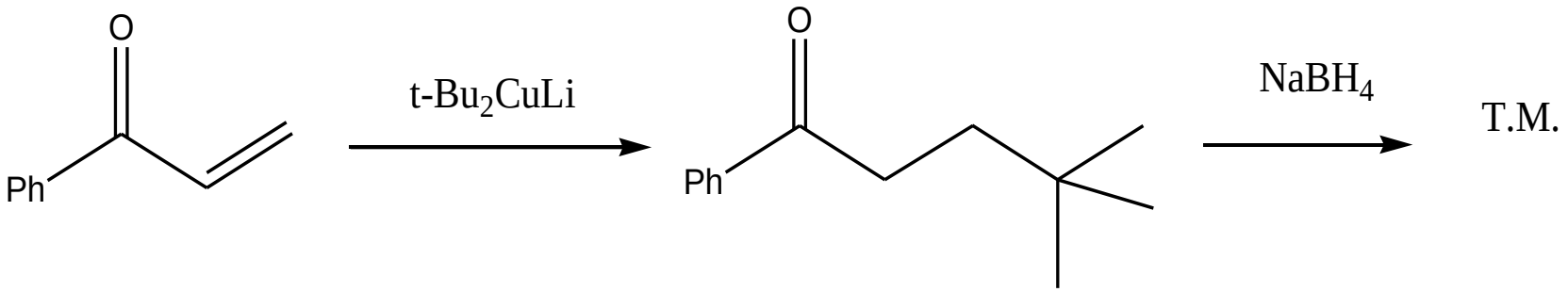
synthesis number four



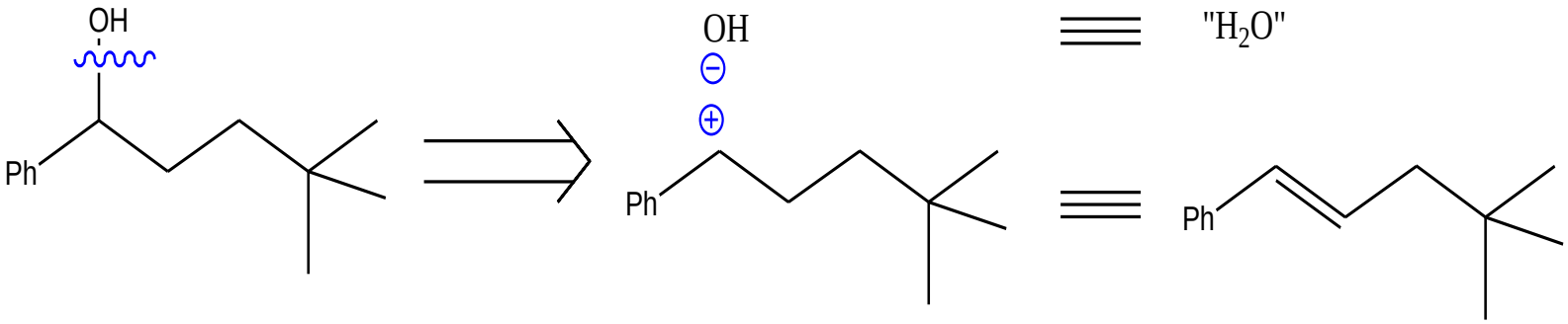
Analysis numbers five:



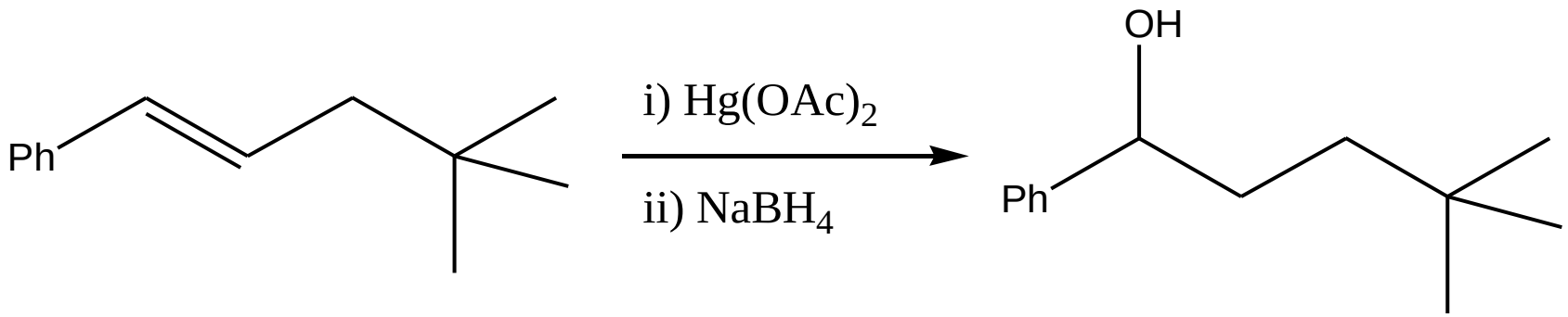
Synthesis number five:



Disconnecting heteroatoms can also be a good idea:



6th approach:



There are other possibilities, but let's not bother with any more. How do you choose which method?

Personal choice. If you have a favorite reagent, or if you are familiar with a particular reaction (or if you have a strong aversion to a reaction/reagent) then this will affect your choice.

Also you need to bear in mind the efficiency of the reactions involved, and any potential side reactions (for example, self-condensation of PhCOMe in method 4).